REMARKS

I. Status of the Claims

Claims 1-3, 5-7, 9-11, 13, 16-18, 20, 23, 25-46, 50-63, 66-72, 83-126, 143, 152-164 and 167-186 were pending with the August 1, 2011 Office Action. Of those, claims 1, 5, 16-18, 20, 23, 25-29, 33-46, 50-63, 66-72, 83-126, 143, 152-164, 167, 185 and 186 were withdrawn and claims 2, 3, 6, 7, 9-11, 13, 30-32, 169-176 and 178-184 were examined in the Office Action. With this Reply, claims 2, 9, 10, 25-29, 31, 171-173, 182-186 are amended, claim 187 is newly added (and withdrawn) and claims 1, 3, 5-7, 13, 16-18, 20, 23, 30, 33-46, 50-63, 66-72, 83-126, 143, 152-164, 167-170 and 174-176 are newly canceled. The claim cancelations, amendments and addition are made without prejudice or disclaimer and provide no new matter. Claims 2, 9-11, 25-29, 31, 32, 171-173, and 177-187 are now pending. Of those, claims 2, 9-11, 31, 32, 171-173, and 178-184 are presented for reconsideration.

II. Rejection under 35 U.S.C. § 112, First Paragraph - Enablement

The claims are rejected under 35 U.S.C. 112, first paragraph, as not being enabled. Applicants request reconsideration and withdrawal of this rejection in light of the claim amendments and the following comments.

The claims as amended are directed to

A method for the treatment of an immune-related or immune-mediated disorder or disease in a mammalian subject in need of such treatment, the method comprising

(a) obtaining NKT cells from said mammalian subject or another subject;
(b) *ex vivo* educating the NKT cells; and
(c) re-introducing to said subject the educated NKT cells obtained in step (b),

wherein the NKT cells are educated by culturing the cells in the presence of

(a') homogenized tissue of the type affected by the disease,
(b') at least one liver-associated CD4+ or CD8+ lymphocyte of a tolerized subject suffering from said immune-related or immune-mediated disorder, or
(c') a combination of (a') and (b');

wherein the immune-related or immune-mediated disorder or disease is autoimmune liver disease, inflammatory bowel disease, Crohn's disease, graft vs. host disease, graft vs. host-associated liver disease, obesity, diabetes

mellitus, metabolic syndrome, glucose intolerance, or non-alcoholic steatohepatitis.

The enablement of the amended claims would be understood by a skilled artisan after reviewing the specification, in particular the experimental results described at para. **[0344]**-**[0481]** of the specification as published as US 2005/0069546. Specifically, Example 7, at para. **[0344]**-**[0362]** teaches that "...culturing NK1.1+ T cells in the presence of disease associated antigens (subgroup E"5) leads to cytokine pattern that is similar to that of tolerized cells as manifested by increase IL10 secretion." (para. **[0355]**). The Office Action at p. 6, apparently doubts this conclusion, asserting that the increased IFNγ secretion would not be discounted, based on "the teachings of the instant specification as a whole and the knowledge in the art...". However, as discussed in the replies dated January 11, 2010 and October 27, 2010, a close examination of the data supports the conclusion in the specification, since, among the TNBS+ colitis mice, the control (uneducated, untolerized) NKT cells (treatment E"2) had IFNγ=0 and IL10=52, while the NKT cells from orally tolerized mice (E"3) had IFNγ=0 and IL10=230, and the *ex vivo* educated cells (E"5) had IFNγ=38 and IL10=340. Since both oral tolerization and *ex vivo* education increased IL10 levels significantly above that of the uneducated, untolerized cell levels and the E"5 treated cells only secreted an insignificant amount of IFNγ, the skilled artisan would agree that NKT cells from *ex vivo* educated mice are similar to the NKT cells from tolerized mice and have improved anti-inflammatory cytokine levels over the NKT cells from the control mice. The skilled artisan would also understand that a rigid comparison based on the IL10/IFNγ ratio would have limited value in this case, since the IFNγ level in the control cells is 0, making the IL10/IFNγ level "infinity". As such, it is clear that the rigid comparison proposed in the Office Action has no value in comparing the anti-inflammatory value of the cells, since the control cell IL10/IFNγ level is the same as the tolerized cell IL10/IFNγ level (infinity), even though the tolerized cell has more than four times the anti-inflammatory cytokine level and would thus be expected to provide a greater anti-inflammatory response than the control cells. Additionally, the Examples at para. **[0302]**-**[0320]** show that NKT cells of tolerized mice often have IFNγ, since NKT

IL4/IFNγ ratios for those mice are not infinity. Thus, the conclusion of the Applicants, that the *ex vivo* educated NKT cells are similar to the tolerized NKT cells is valid, since both have much higher anti-inflammatory cytokine secretion than the control cells while the *ex vivo* educated NKT cells only secrete a small amount of IFNγ, which is often present in NKT cells from tolerized mice.

The Action, at pp. 6-8, also objects to the breadth of the tissue extract recited to be used for *ex vivo* educating the NKT cells in the claims. In this regard, Applicants note that the claims as amended recite educating the NKT cells with "homogenized tissue of the type affected by the disorder or disease." The extract recited in the claims as amended is thus essentially what was used in the specification examples, *e.g.*, the CEP as described in para. **[0270]** of the specification publication (US 2005/0069546) and the liver tissue extract described at para. **[0402]**, since the tissue extract recited in the claims has all components of the tissue, similar to the extracts in the examples.

Regarding the statement at p. 9 of the Office Action that "...the instant specification provides no working example showing the ex vivo educated NKT cells of example 7 (E"5) can indeed be used to treat an 'immune-related or immune-mediated disorders or diseases in a mammalian subject in need of such treatment,'" Applicants assert that the skilled artisan would understand that the claims are enabled because

- "Example 1" at para. **[0302]-[0309]** and "Example 4" at para. **[0321]-[0331]** show that oral tolerization is an effective treatment for colitis;

- "Example 7" at para. **[0344]-[0358]** teaches that "...culturing NK1.1+ T cells in the presence of disease associated antigens (subgroup E"5) leads to cytokine pattern that is similar to that of tolerized cells as manifested by increase IL10 secretion" (as discussed above); and

- The examples at para. **[0359]-[0481]** demonstrate that adoptive transfer of ex vivo educated NKT cells is a useful treatment for various diseases and disorders, similar to oral tolerization.

With the above findings, the skilled artisan would understand that adoptive transfer of CEP-treated ex vivo educated NKT cells would have similar effectiveness against colitis as oral tolerization.

At p. 7-8, the Office Action continues to assert that mouse NKT cells are so different from human NKT cells that mouse models of NKT cell behavior could not be extrapolated to humans. In the previous response, Applicants provided two references (Galli and Van Kaer) where mouse NKT cells were used to make predictions for human disease and human NKT cell responses. The current Office Action did not accept the evidence provided by those references since they were published after the priority date for the instant application (December 24, 2001). In response, Applicants provide four references herewith, dated prior to the instant priority date, where mouse disease models involving NKT cell responses are evaluated. The references are:

- Singh et al., 2001, J. Exp. Med. 194:1801-1811, demonstrating that NKT cell activation protects mice against experimental autoimmune encephalomyelitis, a model for multiple sclerosis;

- Kakimi et al., 2001, J. Immunol. 161:6701-6705, teaching that inhibition of hepatitis B virus replication by activated NKT cells in mice does not require inflammatory cell recruitment;

- Yang et al., 2001, Diabetes 50:2691-2699, teaching that intrinsic defects in the T cell lineage results in NKT cell deficiency and the development of diabetes in mice; and

- Fort et al., 1998, J. Immunol. 161:3256-3261, teaching that NK1.1 cells are regulators of $CD4^+$ T cells in a mouse colitis model.

The above four references unequivocally evaluate NKT cells in mouse models of human disease, establishing that, at the time of filing, mouse NKT cells were established models of human NKT cells. As instructed in MPEP 2164.02,

> ...if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Since the above 4 references utilize NKT cell behavior of mouse disease models as predictive of human NKT cell behavior, mouse NKT cells were considered analogous to

human NKT cells in mouse models of several human diseases, including colitis, and the use of mouse NKT cells as models for human NKT cells was clearly established at the earliest priority date. Clearly, the differences between mouse and human NKT cells as espoused by the Office were small enough where skilled artisans (*i.e.*, the authors of the above references) did not consider them to negate the value of the mouse models for predicting human NKT cell behavior.

In light of the above discussion, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, enablement requirement, is respectfully requested.

III. Rejection under 35 U.S.C. § 112, Second Paragraph - Indefiniteness

Claims 2, 3, 172 and 173 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Office asserts that, since the claims read "proteins extracted from tissue affected by the immune-related disorder" such tissue could not be healthy tissue, as recited in claim 172, and claim 173 does not further limit the claim.

Applicants request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

The claims as amended recite "...the NKT cells are educated by culturing the cells in the presence of (a') homogenized tissue of the type affected by the disease...", making clear that the tissue could be healthy tissue or diseased tissue. The skilled artisan would understand that Applicants contemplated at the time of filing that healthy tissue could be utilized in the NKT cell education, since liver extracts from normal mice were used at least in the experiment described at para. **[0434]-[0437]** of the specification as published as US 2005/0069546.

III. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections of record and examination of the withdrawn claims 25-29, 177 and 185-187, which are encompassed by linking claim 2.

Applicants authorize the United States Patent and Trademark Office to charge all fees required to maintain pendency of this application, including the extension of time and Request for Continued Examination fees, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,

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